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In This Issue

Daptomycin (Cubicin™): A Brief Review

Daptomycin is a new lipopeptide antibiotic indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible strains only). Daptomycin is not indicated for the treatment of pneumonia.[1]

Clinical Pharmacology

Daptomycin is a cyclic semisynthetic lipopeptide (peptolide) antibiotic with activity limited to gram-positive organisms. It is derived from the fermentation of *Streptomyces roseosporus*.[2,3] Its mechanism of action possibly involves disrupting amino acid transport by the cell membrane and altering cytoplasmic membrane potential. Daptomycin binds to bacterial membranes and causes a rapid depolarization of membrane potential. The loss of membrane potential results in inhibition of protein, DNA and RNA synthesis, and ultimately to cell death.[1,4]

Rabeprazole Replaces Omeprazole as Formulary Proton-Pump Inhibitor of Choice

After consulting with NIH experts in the field of gastroenterology, the Pharmacy & Therapeutics Committee recently approved a switch from Prilosec (omeprazole) to Aciphex (rabeprazole) on the Clinical Center Drug Formulary. Rabeprazole, which was approved for use in the U.S. in 1999, has a similar safety and efficacy profile compared to omeprazole.

While most experts consider the proton-pump inhibitors to be therapeutically equivalent, the cost of these agents can vary substantially. In 2003 alone, the Clinical Center spent $680,032.00 on Prilosec 20 mg capsules. This drug is widely used by all institutes and clinical services for a number of different indications. The current NIH contract price for omeprazole is $2.39 per 20-mg capsule, and approximately 24,000 capsules are used per month. A generic omeprazole capsule (AB-rated by the FDA) is available in a bottle of 30 at a price of $1.31 per capsule.

Rabeprazole (Aciphex) 20 mg, is available to the NIH and other federal hospitals at a contract price of $0.64 per enteric-coated tablet. The economic impact from switching all Prilosec use to rabeprazole should realize an annual savings of as much as $500,000.00.

The switch from omeprazole to rabeprazole will be done in a phased fashion beginning with new orders. Omeprazole has been deleted from the formulary, but the drug name will remain in the MedsIndex of the MIS for 6-12 months. Rabeprazole ordering screens have already been added. Physicians who select omeprazole will receive a message informing them of the CC decision to switch to rabeprazole. The same MIS screen will offer the option to order the new drug. Omeprazole (in the generic form) will continue to be available for a few patients who remain in an ongoing Zollinger-Ellison Syndrome protocol.

It has concentration-dependent bactericidal activity against a variety of gram-positive organisms including methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis*, vancomycin-intermediate *S. aureus*, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant *Enterococcus* species.[2,3,5-12] It has also demonstrated *in vitro* activity against *Corynebacterium* spp., Peptostreptococcus, *Eubacterium* spp., *Propionibacterium* spp., *Clostridium perfringens*, *Clostridium difficile*, *Clostridium innocuum*, including strains of vancomycin-resistant *C. innocuum* and strains of linezolid-resistant and quinupristin/dalfopristin-resistant *C. difficile*.[5,13] Daptomycin MIC90s for methicillin-resistant *S. aureus* have been 0.25 to 1 mcg/mL.[2,6,7,14,15,16] The daptomycin MIC90 has been consistently 2- to 4-fold lower than that of vancomycin for methicillin-resistant and methicillin-susceptible *S. aureus.*, methicillin-resistant and methicillin-susceptible *S. epidermidis*, *S. pyogenes*, *Staphylococcus haemolyticus*, *S. pneumoniae*, *E. faecalis*, and *E. faecium*.[2,3,6,7,14,15,17] Against vancomycin-sensitive and vancomycin-resistant *E. faecalis*, daptomycin was similar to or more active than linezolid, and more active than quinupristin-dalfopristin, and vancomycin.[3,18] Daptomycin has demonstrated activity against clinical isolates of linezolid/vancomycin-resistant *E. faecium*.[19] It has equivalent activity against vancomycin-susceptible and vancomycin-resistant isolates of *E. faecalis* and *E. faecium*, as well as equivalent activity against multidrug-resistant and multidrug-susceptible strains of *S. pneumoniae*.[7,11,16,20,21] Oxacillin-resistance in staphylococci, vancomycin-resistance and quinupristin/dalfopristin-resistance in enterococci, and penicillin-resistance in *S. pneumoniae* were not observed to influence daptomycin activity.[22] No major difference in the MIC distribution for daptomycin was observed between multidrug-resistant and non-multidrug-resistant isolates of *S. aureus*, *E. faecalis*, *E. faecium*, and *S. pneumoniae*.[7] Daptomycin activity against linezolid-resistant strains of *E. faecalis*, *E. faecium*, and *S. aureus* did not differ from daptomycin activity against linezolid-susceptible strains.[23] Daptomycin has demonstrated a post antibiotic effect against staphylococcal organisms with a mean duration of 2.5 hours and a pneumonococcal post antibiotic effect of 1.7 hours.[24]

Daptomycin was effective in animal models of septicemia induced by methicillin-resistant *S. aureus*, methicillin-sensitive *S. aureus*, *S. pneumoniae*, and vancomycin-resistant enterococcus.[25] Daptomycin activity was also observed in vancomycin-intermediate *S. aureus*, vancomycin-resistant *E. faecium*, and methicillin-resistant *S. aureus* from simulated sequestered infection sites.[10] It was also effective in animal models of infections of soft tissue, kidneys, heart, lungs, and bone caused by gram-positive strains, including methicillin-resistant *S. aureus* and vancomycin-resistant enterococci.[26-30] In an intraperitoneal systemic murine infection model, daptomycin demonstrated activity against vancomycin-intermediate *S. aureus*, methicillin-resistant *S. aureus*, and methicillin-susceptible *S. aureus* infection.[17] In peritoneal dialysate fluid, daptomycin demonstrated increased bacterial killing compared with cefazolin and vancomycin against methicillin-resistant *S. aureus*, methicillin-susceptible *S. aureus*, methicillin-susceptible *S. epidermidis*, and *Streptococcus sanguis*, suggesting a possible role for this agent in the therapy of peritoneal dialysis peritonitis.[31]

Daptomycin has demonstrated synergistic activity with rifampin and ampicillin against vancomycin-resistant enterococci, and with gentamicin against staphylococci and enterococci.[32] The combination of daptomycin with linezolid or quinupristin/dalfopristin resulted in additive activity against vancomycin-resistant *E. faecium*.[33] Daptomycin plus rifampin demonstrated greater activity than either agent alone in an animal model of endocarditis due to methicillin-resistant *S. aureus*.[30]

Spontaneous resistance to daptomycin occurs rarely. Resistant organisms have been isolated by serial passage in liquid media containing subinhibitory daptomycin concentrations. Organisms developing resistance tended to be less virulent and did not demonstrate cross-resistance to other antimicrobial agents.[4,26] No mechanism of resistance has been identified, and no known transferable elements cause daptomycin resistance.[1]

The presence of calcium cations is necessary for the antibacterial activity of daptomycin. When performing *in vitro* daptomycin testing, the medium should contain added calcium approaching the concentration of ionized calcium present normally in human serum (approximately 50 mg/L in broth medium and a minimum of 28 mg/L in agar medium). This is a higher concentration of calcium than is present in the National Committee for Clinical Laboratory Standards (NCCLS) recommended cation-adjusted Mueller-Hinton broth (20 to 25 mg Ca^{2+}/L) used in the susceptibility testing of other agents.[5,34] Dilution testing requires the use of daptomycin susceptibility powder.[1] Susceptibility criteria are summarized in Table 1. *In vitro*, the greatest bactericidal effect has been apparent at daptomycin concentrations eight times the MIC.[2] Significant bactericidal activity has been observed at concentrations 2 to 6 times the MIC.[8,35]

Table 1. Susceptibility Criteria[1]

Pathogen	Minimal Inhibitory Concentration	Disk Diffusion Zone Diameter
S. aureus (MSSA & MRSA)	≤ 1 mcg/mL	≥ 16 mm
S. pyogenes, *S. agalactiae*, and *S. dysgalactiae* subsp. *equisimilis*	≤ 1 mcg/mL	≥ 16 mm
E. faecalis (vancomycin-susceptible)	≤ 4 mcg/mL	≥ 11 mm

An absence of data on resistance precludes setting standards for intermediate or resistant; organisms testing nonsusceptible should be retested, and if confirmed nonsusceptible sent to a reference laboratory for further testing.

Pharmacokinetics

A peak concentration of 52 to 77 mg/L was achieved following a single 4 mg/kg intravenous dose in healthy volunteers.[36,37] With intravenous doses of 1 mg/kg and 2 mg/kg, peak concentrations were 11 and 20 mcg/mL, respectively. At 24 hours after administration, the daptomycin serum concentration was 1.5 to 1.9 mcg/mL in recipients of a 2 mg/kg dose.[35,38] At steady-state in patients receiving daptomycin 3 mg/kg every 12 hours in the therapy of bacterial endocarditis or bacteremia, the mean peak concentration was 35 mg/L and the mean trough level was 8.88 mg/L.[39] At steady-state in healthy subjects receiving daptomycin 4 mg/kg, 6 mg/kg, or 8 mg/kg once daily, the peak concentrations were 57.8 mcg/mL, 98.6 mcg/mL, and 133 mcg/mL, respectively; trough concentrations were 6.37 mcg/mL, 9.13 mcg/mL, and 15.3 mcg/mL, respectively. With once-daily dosing, pharmacokinetics are linear up to a dose of 6 mg/kg.[26,40] At a dose of 8 mg/kg, the area under the curve (AUC) and trough concentration were not linear; peak concentrations were 2.2-fold greater than those observed at the 4 mg/kg dose.[40]

In cantharidin-induced inflammatory fluid, mean concentrations of 9.4, 14.5, and 27.6 mcg/mL were observed at 1, 2, and 3.7 hours, respectively, after intravenous administration of a 4 mg/kg intravenous dose.[41] In animal studies daptomycin was observed to be retained in the kidneys, but did not penetrate the blood-brain barrier.[1]

Daptomycin is 87% to 96% plasma protein bound. It is bound primarily to serum albumin, in a concentration-independent manner.[1,6,26,36,39,40] Protein binding was reduced to 87.6% in patients with creatinine clearance less than 30 mL/min, 85.9% in hemodialysis patients, and 83.5% in patients undergoing continuous ambulatory peritoneal dialysis.[1] Protein binding was not observed to be altered in patients with hepatic impairment.[1] Volume of distribution is approximately 0.1 L/kg.[40] The distribution of daptomycin into the extravascular fluid is influenced by body weight.[42]

Daptomycin has a 7- to 11-hour plasma elimination half-life.[3,38,41] The half-life from the inflammatory exudate was 17.3 hours (range 6.3 to 32 hours).[41] The long half-life and a dose-dependent post-antibiotic effect of 1 to 6 hours make once-daily dosing possible.[3]

Excretion is primarily renal with 60% to 78% of the total dose recovered in the urine.[26,36,38,41] Up to 60% of the dose is excreted in the urine as unchanged drug.[26,36,40] Daptomycin undergoes some extrahepatic metabolism to inactive metabolites.[36] Daptomycin does not inhibit or induce CYP isozymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, or 3A4; therefore, it is unlikely that daptomycin will influence the metabolism of other medications metabolized via the CYP enzymes. It is not known if daptomycin is a substrate of the CYP system.[1]

The pharmacokinetics of daptomycin are not altered in patients with moderate renal impairment (CrCl greater than 30 mL/min). In nondialysis subjects, a linear relationship was observed between calculated creatinine clearance and daptomycin clearance. In patients with creatinine clearance less than 30 mL/min, and patients with end-stage renal disease on hemodialysis or peritoneal dialysis, the half-life was increased to approximately 30 hours. Dosage adjustments are necessary in this population.[37]

Gender differences in the pharmacokinetics of daptomycin have not been apparent.[40] The pharmacokinetics of daptomycin is not altered in subjects with moderate hepatic impairment. It has not been studied in patients with severe hepatic impairment.[1] In elderly subjects daptomycin total clearance was reduced 35% and the AUC was increased 58% compared to young healthy subjects; however, no dosage adjustment is necessary in elderly patients with normal renal function.[1] In obese subjects daptomycin pharmacokinetics were also modestly altered (plasma clearance increased 18% to 46% and AUC increased 30% to 31%); however, no dosage adjustments are necessary.[1] Daptomycin pharmacokinetics have not been assessed in pediatric patients.[1]

Comparative Efficacy

Approval was based on a New Drug Application containing data from two similarly designed randomized, investigator-blinded, Phase III studies enrolling patients with complicated skin and skin structure infections. In both studies patients were randomized to therapy with daptomycin 4 mg/kg intravenously once daily or standard therapy (semi-synthetic penicillin [nafcillin, oxacillin, cloxacillin, or flucloxacillin] 4 to 12 g/day or vancomycin 1 g every 12 hours intravenously) for a planned treatment duration of 7 to 14 days. The addition of aztreonam or metronidazole was permitted as needed. Patients with known bacteremia at baseline were excluded. Assessment of outcomes and adverse effects was by a blinded investigator at each study site. An unblinded co-investigator adjusted vancomycin doses. Patients could be switched to oral therapy after a minimum of 4 days of intravenous therapy if clinical improvement was documented; however, 89.7% received intravenous medication only.[1,43,44]

One study conducted primarily in the United States and South Africa enrolled 530 patients. Among the patients randomized to standard therapy, 58% received vancomycin. Clinical success in the intent-to-treat analysis occurred in 62.5% (165/264) of daptomycin-treated patients and 60.9% (162/266) of comparator-treated patients. In a modified intent-to-treat analysis (evaluating only those with positive culture for a gram-positive pathogen at baseline), a successful clinical response was observed in 67% of patients in both treatment groups 6 to 20 days after completion of therapy. Clinical success in the clinically evaluable population was documented in 76% (158/208) treated with daptomycin and 76.7% (158/206) treated with a comparator agent. Dosage adjustments were necessary in 46% of vancomycin-treated patients compared with 15% of daptomycin-treated patients. Dosage adjustments in the daptomycin-treated patients were typically a single adjustment based on renal function at study entry.[1,43]

The other study conducted only at sites outside the United States enrolled 562 patients. Among the patients randomized to standard therapy, 85% received a penicillin. By intent-to-treat analysis, successful clinical responses were

observed in 80.4% of daptomycin-treated patients and 80.5% of comparator-treated patients at 6 to 20 days after completion of therapy. Clinical success among clinically evaluable patients was achieved in 89.9% of daptomycin-treated patients and 90.4% (226/250) of comparator-treated patients. At baseline, the median clinical symptom score was 13 in both groups. At day-3 to -4 of treatment, clinical symptom score was reduced to a greater extent in the daptomycin group (median reduction 5 vs 4, $P<0.05$). The median duration of therapy was also reduced in the daptomycin group (7 vs 8 days, $P<0.05$).[1,44]

Overall, a total of 913 patients were clinically evaluable in these two studies; 429 treated with daptomycin, 299 treated with the semi-synthetic penicillin, and 185 treated with vancomycin. In the comparison of daptomycin and the penicillin, clinical success was achieved 85.8% of patients treated with daptomycin (268/312) compared with 88.6% (265/299) treated with the penicillin (95% CI -2.6, 7.8). In the comparison of daptomycin with vancomycin, clinical success was achieved in 81.1% treated with daptomycin (95/117) compared with 73.5% (136/185) treated with vancomycin (95% CI, -15.5, 2).[45] Overall, results were similar regardless of the type of infection (eg, wound infections, major abscess, ulcer infections, and other infections) and infecting pathogen.[1]

Eli Lilly & Co. had conducted early clinical trials with daptomycin in the 1980s and early 1990s. In some early studies daptomycin was reported effective in the treatment of skin and skin structure infections and bacteremia at doses of 2 to 3 mg/kg every 12 hours. However, skeletal muscle toxicity was observed at high doses and treatment failures were observed in bacteremias and *S. aureus* endocarditis prompting Lilly to discontinue product development.[3,14] Case reports described some of these early treatment failures in patients with *S. pneumoniae* and *S. aureus* bacteremias treated with daptomycin 2 mg/kg daily.[46] Treatment failure in endocarditis may have been due to poor penetration of daptomycin into the core of fibrin, a component of the vegetation in bacterial endocarditis.[47] Efficacy was described in a patient treated with daptomycin 2 mg/kg for 5 days for a group A beta-hemolytic streptococci wound infection.[38] Another case report described successful treatment with daptomycin in 2 neutropenic bone marrow transplant patients with catheter-associated *Leuconostoc* bacteremia following a vancomycin treatment failure. One patient with reduced renal function received daptomycin 4.5 mg/kg every 36 hours for 9 days and then 6 mg/kg daily after renal function returned to normal for a total treatment course of 15 days. The other patient received daptomycin 6 mg/kg daily.[48] A renewed interest in the product emerged in response to a need for new agents with activity against vancomycin-resistant organisms. Cubist Pharmaceuticals obtained the rights to daptomycin in 1997 and began clinical trials with a new dosage regimen in 1999.[26]

Contraindications, Warnings and Precautions

Daptomycin is contraindicated in patients with known hypersensitivity to daptomycin.[1]

Reversible musculoskeletal toxicity (muscle weakness, myalgia, and creatinine phosphokinase [CPK] elevations) occurred with high daptomycin doses administered as multiple doses daily in early daptomycin studies. Animal data, and results from studies with once daily dosing in humans, suggest the incidence of musculoskeletal effects may be reduced with once-daily dosing of the same total daily dose.[49] In Phase III clinical trials, elevations in CPK occurred in 2.8% of daptomycin-treated patients compared to 1.8% of patients treated with comparator agents.[1] Patients with baseline elevations in CPK levels did not experience an increased incidence of CPK elevations or myopathy. Patients receiving daptomycin should be monitored for muscle pain or weakness, and CPK levels should be monitored once weekly. Patients developing an increase in CPK should be monitored more frequently. Daptomycin should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with increased in CPK to greater than 1000 units/L (5 times the upper limit of normal), or in patients without symptoms, but with an increase in CPK to 10 times the upper limit of normal. Temporary discontinuation of agents associated with rhabdomyolysis, such as the HMG-CoA reductase inhibitors, should be considered during daptomycin therapy.[1]

Reductions in nerve conduction velocity and adverse effects suggestive of peripheral or cranial neuropathy have been observed in a small number of daptomycin-treated patients. Paresthesias occurred in 0.7% of daptomycin-treated patients and 0.7% of patients treated with comparator agents in clinical trials.[1]

Hypersensitivity reactions (fever, rash, and/or urticaria) occurred less frequently in daptomycin-treated patients than in patients treated with either semi-synthetic penicillins or vancomycin.[43]

Pseudomembranous colitis has been reported in association with daptomycin and should be considered in any patient presenting with diarrhea subsequent to therapy.[1]

Safety and efficacy of daptomycin have not been established in pediatric patients. In daptomycin clinical trials, 27% of patients were 65 years of age or older and 12.4% were 75 years or older. Clinical success rates were lower in patients 65 years of age or older compared to younger subjects, and adverse event rates were greater.[1]

Daptomycin is in Pregnancy Category B. No evidence of harm to the fetus was observed in animal study doses up to 3 and 6 times the human dose based on body surface area. Daptomycin should be used during pregnancy only if clearly needed.[1] It is not known if daptomycin is excreted in human milk. It should be used with caution in nursing women.[1]

Adverse Reactions

Adverse reactions observed in clinical trials have included diarrhea, vomiting, hypersensitivity reactions, dermatitis, sickle cell crisis, myalgia, and creatine phosphokinase elevations.[26,40,41,43,45] The most common adverse effects observed with daptomycin or comparator agents in Phase III studies are summarized in Table 2.[1]

Table 2. Adverse Effects Occurring in 5% or More of Patients Treated with Daptomycin or Comparator Agents[1]

Adverse Event	Daptomycin (N=534)	Comparator* (N=558)
Gastrointestinal		
Constipation	6.2%	6.8%
Nausea	5.8%	9.5%
Diarrhea	5.2%	4.3%
General		
Injection site reactions	5.8%	7.7%
Nervous system		
Headache	5.4%	5.4%
Insomnia	4.5%	5.4%

* Comparator agents: vancomycin and anti-staphylococcal penicillins (nafcillin, oxacillin, cloxacillin, flucloxacillin)

Drug Interactions

When administered with tobramycin 1 mg/kg intravenously, the peak concentration after daptomycin 2 mg/kg was increased 12.7% and AUC was increased 8.7%, while the tobramycin peak concentration was reduced 10.7% and the AUC was reduced 6.6%. Although these differences were not statistically significant, the potential for an interaction with the 4 mg/kg dose of daptomycin is unknown and caution is advised when these agents are administered concomitantly.[1] Renal tubular injury, assessed by brush border enzyme monitoring, was not increased when daptomycin was administered concomitantly with tobramycin.[50]

Drug interactions were not observed between daptomycin and azithromycin, probenecid, simvastatin, and warfarin.[1] Although interactions were not observed with warfarin in studies enrolling volunteers, the manufacturer recommends monitoring INR for the first several days after starting daptomycin therapy until more experience is available.[1] Similarly, although an increased incidence of myopathy was not observed in ten healthy subjects receiving concomitant simvastatin and daptomycin in a drug interaction study, the daptomycin labeling suggests temporarily discontinuing HMG-CoA reductase inhibitors in patients receiving daptomycin.[1]

Dosing

The recommended dose is 4 mg/kg as a 30-minute intravenous infusion in 0.9% sodium chloride injection once every 24 hours for 7 to 14 days.[1]

In patients with renal impairment, the recommended dose is 4 mg/kg every 24 hours for patients with a creatinine clearance of 30 mL/min or greater, and 4 mg/kg every 48 hours for patients with creatinine clearance less than 30 mL/min, including those on hemodialysis or peritoneal dialysis. Daptomycin should be administered following hemodialysis on hemodialysis days.[1]

Product Availability

Daptomycin received FDA approval in September 2003 following a priority review. It is available as a sterile, preservative-free lyophilized powder to be reconstituted with 0.9% sodium chloride injection. It should be stored in the refrigerator (2° to 8°C; 36° to 46°F) in the original package and should be protected from excessive heat. It is supplied in 250 mg and 500 mg single-use vials. The 250 mg vial should be reconstituted with 5 mL 0.9% sodium chloride injection and the 500 mg vials should be reconstituted with 10 mL 0.9% sodium chloride injection. The reconstituted solution should be further diluted with 0.9% sodium chloride prior to administration. Freshly reconstituted solutions range in color from pale yellow to light brown.[1] The reconstituted solution is stable in the vial for 12 hours at room temperature or up to 48 hours under refrigeration (2° to 8°C; 36° to 46°F). The diluted solution is stable in the infusion bag for 12 hours at room temperature or 48 hours under refrigeration. The combined time the vial and infusion bag should be held at room temperature should not exceed 12 hours. The combined time for the vial and bag under refrigeration should not exceed 48 hours.[1]

Conclusion

Daptomycin will offer an additional alternative for the treatment of infections caused by resistant gram-positive organisms. Additional efficacy and safety information will further clarify the role of this agent.

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Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Emtricitabine (Emtriva), an oral antiretroviral
- Dexmedetomidine (Precedex), an injecatble sedative [Use restricted to the operating room and intensive care units]
- Rabeprazole (Aciphex), an oral proton-pump inhibitor

Deletions

None

FDA Safety Alerts

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.

- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov*. In the message body enter: *subscribe medwatch* and your e-mail address.

Drug Information Service

- Patient-specific pharmacotherapy evaluation and management
- Comprehensive information about medications, biologics, and nutrients
- Critical evaluation of drug therapy literature
- Assistance with study design and protocol development
- Clinical trial drug safety monitoring
- Investigational drug information
- Parenteral nutrition assessment and management

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